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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,762	10/12/2001	Margaret Shipp	DFN-031US	2130

959 7590 05/20/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
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1648

12

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/830,762

Applicant(s)

SHIPP ET AL.

Examiner

Ulrike Winkler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 11-19 and 21-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10/12/01 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that It would not be a serious burden to search group II along with group I because the sequences share 71.7% sequence identity and they share functional domains. This is not found persuasive because the search of one sequence will not be coextensive with the other sequence, although the sequences share 70% of their structure they also differ in 30% of their structure, the claims are not limited to only those structures that are shared by both sequences. Therefore, the search fro the sequences will be different.

The requirement is still deemed proper and is therefore made FINAL.

Specification

Applicant is required to update the status (pending, allowed, ect.) of all parent priority applications in the first line of the specification.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 8, is attached to the instant Office Action.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information

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submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 20 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO. 2 encoded by the nucleic acid sequence set forth in SEQ ID NO:1 or 3, does not reasonably provide enablement for an isolated polypeptide or an isolated nucleic acid molecule that is at least 62% or 72% homologues to SEQ ID NO: 1, 2 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

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Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to an isolated polynucleotide encoding a polypeptide of SEQ ID NO: 2 or an isolated polynucleotide encoding a polypeptide which is at least 62% identical to the amino acid sequence in of SEQ ID NO:2. This includes a whole universe of polypeptides with 62% identity to SEQ ID NO.2. The claims are drawn to an isolated nucleic acid comprising SEQ ID NO: 1 or 3 or complement thereof, it is not clear if the complement is a full length complement or if this includes small fragments. The specification included isolated nucleic acid to encompass insertion deletion or substitution (see page 20, lines 14-31), isolated nucleic acids include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). The specification does not prove a measurable biological activity for the nucleic acid molecule, which would define the function of the molecule.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polynucleotide fragment, which encodes a polypeptide fragment with sequence homology to SEQ ID NO: 2 without any biological properties associated with the homologue. Claims drawn to an isolated nucleic acid molecule, which encodes a protein and mutations within the nucleic acid molecule, which may effect the

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amino acid sequence. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" residue at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., Journal of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all nucleic acid fragments with sequence similarity to the amino acid sequence shown in SEQ ID NO. 2. Therefore, in view of the speculative nature of the invention, the lack of predictability of

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the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed, which include variation in the nucleic acid sequence resulting in changes in the encoded protein sequence.

Claims 1-10 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO: 1, 2 and 3 and therefore the written description is not commensurate in scope with the claims which read on allelic variants of SEQ ID NO. 2.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Alleles are one of two or more alternative forms of a gene occupying the same locus on a particular chromosome and differing from other alleles of that locus at one or more mutational sites, which therefore encode allelic variant proteins. Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID

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NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and or encoded variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement, which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification included isolated nucleic acid to encompass insertion deletion or substitution (see page 20, lines 14-31), isolated nucleic acid molecules include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). However, no disclosure, beyond the mere mention of biologically active fragments (i.e. variants) is made in the specification. This is insufficient to support the

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generic claims as provided by the Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

Therefore, only a nucleic acid sequence of SEQ ID No: 1 or 3 encoding the polypeptide sequence of SEQ ID NO. 2 meets the written description provision of 35 USC 112, first paragraph.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Conclusion

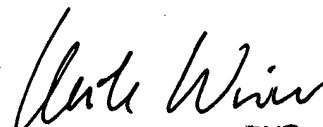
No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


ULRIKE WINKLER, PH.D.
PATENT EXAMINER 5/19/03